6th International Convocation on Immunology
Niagara Falls, N.Y., 1978

Immunopathology

Editors
Felix Milgrom, Buffalo, N.Y.
Boris Albini, Buffalo, N.Y.

S. Karger
Basel · München · Paris · London · New York · Sydney

ISBN 3–8055–2971–6

Sixth International Convocation on Immunology

Niagara Falls, N.Y., June 12–15, 1978

Immunopathology

Editors
Felix Milgrom and Boris Albini,
Buffalo, N.Y.

74 figures and 62 tables, 1979

S. Karger
Basel · München · Paris
London · New York · Sydney

International Convocations on Immunology

1 International Convocation on Immunology. Buffalo, N.Y., 1968
Editors: *N. R. Rose and F. Milgrom*, Buffalo, N.Y.
XXXVIII + 361 p., 140 fig., 93 tab., 1969. ISBN 3-8055-0888-3
2 Cellular Interactions in the Immune Response. Buffalo, N.Y., 1970
Editors: *S. Cohen, G. Cudkowicz and R. T. McCluskey*, Buffalo, N.Y.
VIII + 310 p., 106 fig., 93 tab., 1971. ISBN 3-8055-1202-3
3 Specific Receptors of Antibodies, Antigens and Cells. Buffalo, N.Y., 1972
Editors: *D. Pressman, T. B. Tomasi, jr., A. L. Grossberg and N. R. Rose*, Buffalo, N.Y.
VIII + 412 p., 97 fig., 79 tab., 1973. ISBN 3-8055-1372-0
4 The Immune System and Infectious Diseases. Buffalo, N.Y., 1974
Editors: *E. Neter and F. Milgrom*, Buffalo, N.Y.
X + 549 p., 85 fig., 115 tab., 1975. ISBN 3-8055-2177-4
5 Human Blood Groups. Buffalo, N.Y., 1976
Editors: *J. F. Mohn, R. W. Plunkett, R. K. Cunningham and R. M. Lambert*, Buffalo, N.Y.
XII + 464 p., 97 fig., 94 tab., 1977. ISBN 3-8055-2422-6

National Library of Medicine Cataloging in Publication
International Convocation on Immunology, 6th, Niagara Falls, N.Y., 1978
Immunopathology/editors, Felix Milgrom and Boris Albini.—Basel; New York: Karger, 1979
Sponsored by the Center for Immunology of the State University of New York at Buffalo
1. Immunology—congresses 2. Pathology—congresses I. Milgrom, Felix, ed. II. Albini, Boris, ed.
III. State University of New York at Buffalo. Center for Immunology
W3 IN6856 6th 1978 i/QW 504.3 I5li 1978
ISBN 3-8055-2971-6

Typeset by Asco Trade Typesetting Ltd., Hongkong
Printed in Switzerland by Thür AG Offsetdruck, Pratteln

ISBN 3-8055-2971-6

Sixth International Convocation on Immunology

Organizing Committee

Boris Albini
Giuseppe A. Andres
Ernst H. Beutner
Joseph H. Kite, jr.
Morris Reichlin
Felix Milgrom, Chairman

Acknowledgements

The Center for Immunology and the Convocation Committee gratefully acknowledge the generous contributions in support of this convocation from

Abbott Laboratories
Biological Corporation of America
Biotest-Serum Institut GmbH
Burroughs Wellcome Company
Ciba-Geigy Corporation
Corning Medical
Cutter Laboratories, Inc.
E. I. du Pont de Nemours & Company, Inc.
Hoffmann-LaRoche Inc.
Hooker Chemicals & Plastics Corporation
S. Karger AG
Lederle Laboratories
Mallinckrodt, Inc.
Merck Sharp & Dohme Research Laboratories
Ortho Diagnostics Inc.
Rochester Scientific Company, Inc.
The Squibb Institute for Medical Research
State University of New York at Buffalo
Technicon Corporation
Medical Products Division, Union Carbide Corporation
Wampole Laboratories
Warner-Lambert/Parke-Davis

Introduction

At the beginning of the immunological era, those beneficial immune mechanisms were studied which permit man and animals to recover from infectious diseases and to resist repeated infections.

Jules Bordet was the first to show that not only microorganisms and their products but also completely harmless foreign substances are antigenic and elicit immune responses. Furthermore, he demonstrated that serum of a guinea pig immunized with rabbit red blood cells would cause disease and death when injected into rabbits. This and other observations made *Ehrlich and Morgenroth* coin the term *horror autotoxicus*, 'fear of self-poisoning', to point out that a healthy man or animal would refuse formation of autoantibodies, i.e., antibodies combining with autologous antigens. *Ehrlich and Morgenroth* realized that the lack of formation of autoantibodies is a rather complex phenomenon requiring some immunologic homeostatic mechanisms. As early as 1900 they spoke about the existence of anti-autolysins which prevent the appearance of autolysins and therefore serve as guardians of the *horror autotoxicus* principle. One cannot help admiring these intuitive statements which predicted what we now call anti-idiotypic antibodies and their role in controlling autoimmunity.

Since the very beginning of the 20th century, formation of autoantibodies, both harmful and harmless, was described under natural and experimental conditions. The pathogenic role of immune responses to autologous antigens has been studied by many investigators. In this country, these studies were pioneered by *Ernest Witebsky* and *William Dameshek*. One of the editors of this volume had the unique privilege to co-chair with these two investigators a comprehensive conference on 'Autoimmunity' organized by the New York Academy of Sciences precisely 13 years ago.

Studies on immediate hypersensitivity reactions initiated in 1902 were continued quite extensively. With his description of serum sickness, *von Pirquet* initiated important studies on the pathogenic role of immune complexes.

The pathogenicity of immune mechanisms active in the course of an infectious disease was clearly described in 1890 by *Robert Koch* in his studies on tuberculosis. Thereafter, many instances of immunopathologic lesions in infectious diseases have been documented.

It is rather obvious that immunological mechanisms quite frequently bring more harm

than benefit. Still, it is difficult to condemn the basically teleological immune mechanisms. The damage which they inflict may be conceived as the result of their overeagerness to help, a crime of passion. The field of immunopathology is almost as old as the science of immunology. During over ninety years, studies conducted in this field have made most significant contributions to the practice of medicine.

This book summarizes the proceedings of the *Sixth International Convocation on Immunology*. The organizing committee of this convocation undertook the ambitious goal of preparing a program that would review comprehensively the field of immunopathology. The committee considered it very appropriate that this meeting should be organized by the academic community of Buffalo where immunopathological studies, initiated by *Ernest Witebsky* in the late 1940s, have been conducted in the Department of Microbiology and The Center for Immunology for three decades. The committee succeeded to assemble at this meeting most of the leading research workers in the field. All of them are our friends and many of them had been previously associated with us. It was attempted to achieve a balance between authoritative reviews of well-established concepts and reports on recent data and new hypotheses. We hope that this book will be both informative and provocative. *F. M.*

B. A.

Contents

Immunologically Mediated Systemic Diseases

Immunopathology of Infectious Diseases

Effector Mechanisms in Immunopathology

Workshops

Immunopathology. 6th Int. Convoc. Immunol., Niagara Falls, N.Y., 1978, pp. 1–6 (Karger, Basel 1979)

Is Autoimmunity an Aberration of Physiological Mechanisms?

Pierre Grabar

Institut Pasteur, Paris

All observable pathological phenomena may be exaggerations or inhibitions of physiological mechanisms, with the exception of those cases in which exogeneous agents intervene. Applying this concept, I envisaged the formation of autoantibodies (auto-Abs) not as an aberration of a defense mechanism, but as an exaggeration of a normal physiological mechanism. In simple organisms, nutrition is realized by phagocytosis. This phenomenon exists in all animals, and I assume that it would have disappeared during evolution if it were not necessary. In higher animals, phagocytosis is facilitated by opsonization due to Abs. Thus, one may suppose that Abs participate in a mechanism derived from nutrition. The blood transports many varied and important substances, such as O_2, CO_2, lipids, metals, enzymes, hormones, vitamins, etc., such transport being effected by carriers specific for these substances.

In 1947, and particularly in 1953 at the International Microbiological Congress in Rome [16, 17], I proposed the consideration of the immunoglobulins (at that time known only as 'γ-globulins') as specific 'transporteurs' of metabolic and catabolic products. Evidently, when transporting catabolic products, they are auto-Abs and I assumed that they should be considered as a normal physiological phenomenon.

Some observations can be interpreted as showing the role of Abs as specific 'transporteurs' of metabolites, for example the appearance of Abs to milk proteins in children fed with milk [10], the presence of anti-bovine serum albumin Abs in dogs nourished with beef [18] and mice receiving bovine serum albumin *per os* [2], the reaction of normal sera with glycogen [18], etc. The formation of Abs to nutritional products occurs because these substances escaped total degradation by digestive enzymes.

As mentioned previously, the 'transporteurs' of catabolites are auto-Abs. In a large number of publications, it has been shown that auto-Abs exist normally, that they can appear and that they can be induced experimentally, particularly when Freund's adjuvant is used. In the majority of known cases of the appearance of auto-Abs, destructive or necrotic lesions of certain tissues are observed and the auto-Abs react specifically with components of these tissues [20]. If we assume that, in the particularly interesting case of the NZB mouse, the etiology of the observed anomalies is viral, it is possible to explain the appearance of several different auto-Abs as the virus may attack numerous tissues including the thymus. The experimental induction of auto-Abs against erythrocytes has been achieved in another strain of mice

by the injection of their own red blood cells previously heated to 49 °C [22].

The existence of auto-Abs has been also demonstrated in normal sera, for example: (a) All human sera contain cryoagglutinins [12]. (b) Human serum contains panagglutinins which agglutinate red or white cells of the same organism which have been previously treated with neuraminidase or a protease [34]. These panagglutinins opsonize aging cells, which are then phagocytosed. *Kay* [25] has observed that aged erythrocytes have IgG on their surface. (c) Auto-Abs reacting with degradation products of different classes of immunoglobulin [33] and with fibrinogen cleavage products [32] have been detected in normal human and animal sera. (d) It has been known for a long time that the serum of adult snakes neutralizes their own venom [9]. (e) Nearly all normal sera contain Abs to myelin, which are non-pathogenic [14]. (f) Sera of healthy persons may contain Abs capable of reacting with various tissue extracts, and also with elastin [20], nuclear components [26] and even nucleic acids [9]. Sera of young SJL/J mice also contain antinuclear factors and anti-RNA Abs [7]. In general, the quantity of auto-Abs in human or animal sera increases with age. This may be due to the development of various lesions during life. More auto-Abs can certainly be found in normal sera by the use of very sensitive methods. For example, *Jormalainen and Mäkelä* [24], using the particularly sensitive method of phage labelling, found that normal sera contain Abs reacting with various haptens. Generally, the search for auto-Abs is only undertaken when pathological phenomena are observed, whereas they may also exist in the absence of such phenomena, when routine analysis is not performed. The probable existence of complexes of auto-Abs with autoantigens (auto-Ags) in normal sera may render the detection of auto-Abs more difficult. We may conclude that auto-Abs exist normally and that they can appear as a consequence of abundant tissue destruction, microbial- or viral-induced lesions, thermal injury, etc., and that they may be considered to be an exaggeration of a normal physiological mechanism, the formation of 'transporteurs' of catabolic products.

In an attempt to explain the mechanism involved, I will consider two of the important steps in Ab formation; the first of which is the recognition of the immunogenicity of the Ag and the last step which is the actual synthesis of a specific Ig, a process which is certainly dependent upon genetic information.

It is well known that rabbits, in contrast to mice, do not form Abs to pneumococcal polysaccharides when injected with purified polysaccharides, but form such Abs well when injected with pneumococci. Thus, they possess cells capable of synthesizing these Abs, and if they do not respond, there must be another reason. In addition, it is known that some children are incapable of forming certain Abs. The same also exists in certain animal species or strains. These cases could be explained as being due to a genetic absence of cells capable of synthesizing the corresponding Abs, but it seems established [5] that the genetic factors influencing the formation of Abs to certain Ags relate to the activity of T cells and not the B cells which actually synthesize the Ab molecule. Thus, in these cases genetic control intervenes in the mechanism of Ab formation at a step other than the final synthesis of the Ab molecule. The existence of genetic enzyme deficiencies are well known [13], and we may suppose that they interfere with the normal immunological mechanisms. Whatever the final step of Ab formation, however, the actual synthesis must be the same for Abs to both self and non-self Ags and cells capable of such synthesis must be present normally since the appearance of both categories of Abs can be induced experimentally.

For many years and again recently [19, 20], I have proposed that the simplest explanation of self recognition is that under normal conditions, self Ags are degraded and lose their immunogenicity. In cases where this degradation does not occur and the auto-Ags remain intact, they are immunogenic. Recently, *Mehta* [29] proposed a concept similar to my old hypothesis.

In pathological cases of auto-Ab formation, as mentioned earlier, abundant destruction of cells or tissues can generally be observed. The degradation of their constituents by autolytic enzymes is inhibited because the excess of substrates inhibits the enzymatic activity and, consequently, these constituents retain their immunogenicity. In experimentally induced auto-Ab formation, Freund's adjuvant is almost always used. As has been established, this adjuvant inhibits proteolytic enzymes [27] and thus the degradation of auto-Ags can be avoided and their immunogenicity preserved.

Enzymatic processes have been observed to play an important role in immunogenicity, for example: (a) *Ryan and Lee* [35] found a correlation between resistance to protein degradation by macrophages and immunogenicity. (b) The formation of Abs to nucleic acids can be achieved if these substances are injected in a form in which they are not degraded by nucleases, whereas, if injected in a pure form, degradation occurs and no Abs are produced [31]. (c) *Sela et al.* [36] have observed that the formation of Abs to a certain polypeptide in different strains of mice depends upon differences in the rate of metabolism of this Ag. (d) The importance of the rate of metabolic degradation of erythrocytes and of some bacterial Ags in the antibody response of high and low Ab producer strains has been studied by *Biozzi et al.* [8]. In both cases, slower degradation favors the formation of Abs.

It is well known that it is easier to induce auto-Abs when modified auto-Ags or cross-reacting Ags are used. This again seems to indicate that it is the immunogenicity which is important. Cells capable of forming auto-Abs are present, but the metabolism of the modified Ags used may be different from that of the native Ags, thus explaining the difference in response. We may conclude that the role of enzymes is very important in the first step of auto-Ab formation, that is the immunogenicity of self Ags. This concept is particularly simple, based on well-known facts, and does not need particular *ad hoc* hypothesis. It does not, however, exclude some other possible mechanisms.

In the induction of experimental tolerance, it is assumed that the Ag can exist in a tolerogenic form, but the characteristics of this form are not well established. The simplest example is probably that in which non-polymerized IgG can act as tolerogen whereas the polymerized molecule does not induce tolerance. It is thus possible that auto-Ags could also exist in a tolerogenic form, for example, as partially degraded molecules. *Ada et al.* [1] induced tolerance to an undegraded Ag by use of its degradation products and *Benjamin and Hershey* [6] with degradation products of bovine serum albumin. At the present time, it remains uncertain if, in general, Ags must act as a complete molecule or must first be degraded. For example, according to *Ault et al.* [4], non-metabolizable Ags can induce tolerance; this can be interpreted as suggesting that the Ag must be metabolizable to be immunogenic. On the other hand, we have induced Abs in the rabbit to hidden groupings of a native protein [15] which would mean that this Ag was modified following injection.

Although the exact process of activation of the immunocompetent cell is not well established, the possibility exists that a tolerogen can block this mechanism. With Mrs. *Escribano*, we have shown that the formation

of Abs specific for a chemical hapten in rats by their immunization with this hapten coupled with a carrier protein can be inhibited by previous injections of the same free and non-reactive hapten [21]. Thus, a small molecule containing only one determinant group is capable of inducing a certain degree of tolerance. The same mechanism may occur with incompletely degraded self Ags.

Calne et al. [11] have shown that a prolongation of renal allograft survival in pigs can be obtained by injections of large quantities of serum or of spleen extracts. In human transplantation, previous multiple transfusions (particularly of donor serum) enhance graft survival. *Hasek et al.* [23] have induced graft tolerance in the rat by the injection of sera from donor strain rats. Experiments performed by *Feldman* and co-workers [37] have shown that serum constituents can inhibit the sensitization of self cells. Components possessing the specificity of transplantation Ags have been detected in and even isolated from the serum [30]. These substances may act as tolerogens and are probably degradation products of histocompatibility Ags.

Many different explanations of autoimmunization have been proposed. I think that the theory of forbidden clones and the intervention of somatic mutations in the mechanism of autoimmunization have been abandoned. I exclude also the proposed idea that auto-Ags must be modified and thus become in some way foreign to the organism. It is true that modified self Ags more readily induce auto-Abs, but these Abs once formed exhibit equal reactivity with the unmodified determinants of the native Ag. It has also been suggested that auto-Abs are formed following the uncovering of self Ags which normally have no contact with immunocompetent cells. However, we now know that auto-Abs are also formed against tissues in continuous contact with the blood, such as liver [3], or even Igs [33] and serum albumin [28]. Thus this suggestion cannot be proposed as a general mechanism, although hidden self Ags are possibly more highly immunogenic.

On the contrary, it is evident that suppressor cells, their products and thymic hormones play an important role. If the soluble suppressor factors are Ag-specific, it is possible that they modulate the immunogenicity of auto-Ags and that enzymatic processes may be involved. They may, however, act at another step in the mechanism of Ab formation, but this problem will be considered in other reports.

In summary, my concept is that the self-recognition is mainly enzymatic. Under normal conditions, auto-Ags are degraded by autolytic enzymes and become non-immunogenic or possibly tolerogenic. In cases of tissue destruction provoked by exogenous agents, however, the abundance of available tissue components inhibits the activity of the enzymes present. The non-degraded self Ags are immunogenic, and induce auto-Ab formation. The actual synthesis of the specific Igs is the same for Abs to both self and non-self Ags. In both cases, the main role of these Abs is the cleaning up of the organism, and thus, they participate in the same physiological mechanism as 'transporteurs' of metabolic and catabolic products. This concept does not exclude the intervention of suppressor cells and of thymic factors, which may even participate in the mechanism described.

References

1 Ada, G. L.; André, C.; Lambert, R.; Bazin, H., and Heremans, J. F.: The tissue localization, immunogenic and tolerance-inducing properties of antigens and antigen fragments. Cold Spring Harb. Symp. *32:* 381–393 (1967).

2 André, C.; Parish, C. R.; Nossal, G. J. V., and Abbot, A.: Interference of oral immunization with the intestinal absorption of heterologous albumins. Eur. J. Immunol. *4:* 701–704 (1974).

3 Arnason, B.; Salomon, J. C. et Grabar, P.: Anticorps antifoie et anti-immunoglobulines sériques chez les souris classiques et axéniques; étude comparative par nécrose aiguë provoquée par le tetrachlorure de carbone. C. r. hebd. Séanc. Acad. Sci., Paris *259:* 4882–4885 (1964).

4 Ault, K. A.; Unanue, E. R.; Katz, D. H., and Benacerraf, B.: Failure of lymphocytes to reexpress antigen receptors after brief interaction with a tolerogenic *D*-amino acid copolymer. Proc. natn. Acad. Sci. USA *71:* 3111–3114 (1974).

5 Benacerraf, B.: The genetic mechanisms that control the immune response and antigen recognition. Annls. Immunol. Inst. Pasteur, Paris *125C:* 143–164 (1974).

6 Benjamin, D. C. and Hershey, C. W.: The termination of immunological unresponsiveness to the cyanogen bromide fragments of BSA in rabbits J. Immun. *113:* 1593–1598 (1974).

7 Bentwich, Z.; Bonavida, B.; Peled, A., and Haran-Ghera, N.: Evaluation of auto-antibodies and serum abnormalities in SJL/J mice (abstr.). Israel J. med. Scis. *8:* 670 (1972).

8 Biozzi, G.; Stiffel, C.; Mouton, D.; Bouthillier, Y. et Decreusefond, C.: La régulation génétique de la synthèse des immunoglobulines au cours de la réponse immunologique. Annls. Immunol. Inst. Pasteur, Paris *125C:* 107–142 (1974).

9 Boquet, P.: Venins des serpents (Flammarion, Paris 1948).

10 Burgin-Wolff, A. und Gerger, E.: Die Bildung von Antikörpern gegen verschiedene Kuhmilch-Proteine bei Neugeborenen, Kindern, Erwachsenen und Graviden. Experientia *19:* 22–23 (1963).

11 Calne, R. Y.; Davis, D. R.; Hadjiyannakis, E.; Sells, R. A.; White, D.; Herbertson, B. M.; Millard, P. R.; Joysey, V. C.; Davies, D. A. L.; Binns, R. M., and Festenstein, H.: Immunosuppressive effects of soluble cell membrane fractions, donor blood and serum on renal allograft survival. Nature, Lond. *227:* 903–906 (1970).

12 Dacie, J. V.: Occurrences in normal human sera of 'incomplete' forms of cold auto-antibodies. Nature, Lond. *166:* 36 (1950).

13 Dreyfus, J. C.: Bases moléculaires des maladies enzymatiques génétiques. Biochimie *54:* 559–571 (1972).

14 Edington, T. S. and Delessio, D. J.: The assessment by immunofluorescence methods of humoral anti-myelin antibodies in man. J. Immun. *105:* 248–255 (1970).

15 Escribano, M. J.; Keilova, H. et Grabar, P.: Etude de la gliadine et de la gluténine après réduction ou oxydation. Biochim. biophys. Acta *127:* 94–100 (1966).

16 Grabar, P.: Les globulines du sérum sanguin (Desoer, Liège 1947).

17 Grabar, P.: Mise en évidence par hémagglutination passive de réactions de divers sérums normaux avec quelques substances macromoléculaires. 6th Congr. Int. Microbiol., Rome 1953, vol. 2, pp. 303–304.

18 Grabar, P.: Réaction de divers sérums normaux avec des substances macromoléculaires naturelles ou synthétiques. Annls. Inst. Pasteur, Paris *88:* 11–23 (1955).

19 Grabar, P.: Formation d'auto-anticorps et leurs activités. Annls. Inst. Pasteur, Paris *118:* 393–402 (1970).

20 Grabar, P.: Hypothesis. Auto-antibodies and immunological theories. Clin. Immun. Immunopath. *4:* 453–466 (1975).

21 Grabar, P. et Escribano, M. J.: Induction de tolérance immunitaire par des haptènes libres non réactifs. C. r. hebd. Séanc. Acad. Sci., Paris *282D:* 1833–1836 (1976).

22 Halpern, B. et Bourdon, G.: Syndrome immunohématologique expérimental ayant des caractères de l'anémie hémolytique autoimmune. C. r. hebd. Séanc. Acad. Sci., Paris *173D:* 2712–2717 (1971).

23 Hašek, M.; Chutná, I.; Holáň, V., and Sládeček, M.: Induction of transplantation tolerance using serum as antigen source. Nature, Lond. *262:* 295–296 (1976).

24 Jormalainen, S. and Mäkelä, O.: Anti-hapten antibodies in normal sera. Eur. J. Immunol. *1:* 471–477 (1971).

25 Kay, M. B.: Mechanism of removal of senescent cells by human macrophages *in situ*. Proc. natn. Acad. Sci. USA *72:* 3521–3525 (1975).

26 Laffin, R. J.; Bardawil, W. A.; Pachas, W. N., and McCarthy, J. S.: Immunofluorescent studies on the occurrence of anti-nuclear factor in normal human serum. Am. J. Path. *45:* 465–479 (1964).

27 Lee, J. W.; Metcalf, R. M., and Ryan, N. L.: Effect of Freund's complete adjuvant on lysosomal enzymes. Int. Archs Allergy appl. Immun. *39:* 609–615 (1970).

28 Lenkei, R. and Ghetie, V.: Methods for detection of antialbumin auto-antibodies in hepatic diseases J. immunol. Meth. *16:* 23–30 (1977).

29 Mehta, N. G.: The crucial role of phagocytosis and lysosomal destruction of antigens. Med. Hypothesis *2:* 141–146 (1976).

30 Oh, S. K.; Pellegrino, M. A.; Ferrone, S.; Sevier, E. D., and Reisfeld, R. A.: Soluble HLA antigens in serum. Eur. J. Immunol. *5:* 161–166 (1975).

31 Plescia, O. J. and Braun, W.: Methylated bovine serum albumin as a carrier for oligo- and polynucleotides; in Plescia and Braun Nucleic acids in immunology, pp. 5–17 (Springer, Berlin 1968).

32 Plow, E. F. and Edgington, T. S.: Immune response

to the cleavage-associated neo-antigens of fibrinogen in man. J. clin. Invest. *56:* 1509–1518 (1975).
33 Rivat, L.: Anti-immunoglobulines humaines. Revue fr. Transfus. *16:* 279–287 (1973).
34 Rosenberg, S. A.; Schwartz, S., and Baker, A.: Natural antibodies to 'cryptic' membrane antigen exposed by treatment with neuraminidase. Behring Inst. Mitt. *55:* 204–208 (1974).
35 Ryan, W. L. and Lee, J. W.: Antigen catabolism by lysosomal enzymes. Immunochemistry *7:* 251–265 (1970).
36 Sela, M.; Mozes, E., and Shaerer, G. M.: Thymus-independence of slowly metabolized immunogens. Proc. natn. Acad. Sci. USA *69:* 2696–2700 (1972).
37 Wekerle, H.; Cohen, I. R., and Feldman, M.: Lymphocyte receptors for auto-antigens; autologous serum inhibits self-recognition. Nature new Biol. *241:* 25–26 (1973).

Dr. P. Grabar, Institut Pasteur, F-75724 Paris Cedex 15 (France)